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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,264	09/30/2005	Eric Francis Morand	BDW003	1609

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EXAMINER	
CHUNG, SUSANNAH LEE	
ART UNIT	PAPER NUMBER
1626	

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11/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,264	MORAND ET AL.	
	Examiner	Art Unit	
	Susannah Chung	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/7/04, 6/30/06, 6/24/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-23 and 26-30 are pending in the instant application. Claims 24, 25, and 31-40 are canceled.

Priority

This application is a 371 of PCT/AU03/00717, filed 06/06/2003.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) by application no. PS 2832 and PS 2834 filed in the Australian Patent Office on 6/7/2002, which papers have been placed of record in the file. The application names an inventor or inventors named in the prior application.

Information Disclosure Statement

The information disclosure statement (IDS), filed on 12/7/04, 6/30/06, and 6/24/08 have been considered. Please refer to Applicant's copy of the 1449 submitted herewith.

Response to Election/Restrictions

Applicant's election without traverse of Group IV in the reply filed on 10/2/2008 is acknowledged. The election of rheumatoid arthritis and benzimidazole-2-one-5n-pentanoate for search and examination purposes is also acknowledged.

Scope of the Elected Invention

Claims 1-23 and 26-30 are pending in this application. All claims will be examined for patentability.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 19, 26, and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrug is found in the specification on page 37. c) There is no working example of a prodrug of a compound the formula (I), (II), (III), or (IV). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Prodrug require a significant amount of research. There is also a low expectation of success. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the specification is relevant. Ultimately, extensive development must be undertaken to find a prodrug. f) Artisans making prodrugs would require a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved, and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula (I) of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by claim 1.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular compound of formula (I) of claim 1 is, in fact, a prodrug.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 and 26-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for the reasons describe below.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

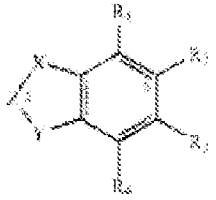
1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to the claims of the present invention below:

(1) The Nature of the Invention

Claim 1 is directed to

1. (original) A method of inhibiting cytokine or biological activity of MIF comprising contacting MIF with a cytokine or biological activity inhibiting effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof



(I)

(2) The Breadth of the claims

Claims 1-23 and 26-30 will be give its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, the claims that do not cite a specific disease will be interpreted to encompass all potential diseases of the receptor cited and claims that are directed to specific diseases will be interpreted to encompass all uses of those diseases, regardless of whether it is a primary or secondary method of use or treating.

(3) The state of the prior art

The state of the pharmaceutical art in general involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat, inhibit or prevent diseases such as rheumatoid arthritis).

The state of the art at the time of this application is that the etiology and treatment of rheumatoid arthritis (RA) and related diseases are not well understood. There is no known cure for RA. The goal of treatment is to reduce joint inflammation/pain, maximize joint function, and prevent joint destruction. Finding a working therapeutic method is challenging and highly unpredictable. Adding to the challenge are the many different types of diseases in addition to RA claimed in the instant application, which all have different mechanisms of action and no two diseases could be said to share the same method of treatment.

Currently, there are two classes of medication being used in treating RA: fast-acting "first-line drugs" and slow-acting "second-line drugs." First-line drugs include aspirin and corticosteroids, while second-line drugs include methotrexates and hydroxychloroquines. It is unclear from the instant specification what type of drug the instantly claimed is.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether a showing of some activity in a very specific cell line could reliably and

predictably applied to the treatment and prevention of all rheumatoid arthritis. There is no absolute predictability, even in view of the high level of skill in the art.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses biological testing data (specification pages 92-109). The data provided shows in vitro and inhibition data in specific assays. For example in vitro assay of MIF antagonism is provided on page 98. More specific data regarding the use of the instantly claimed compounds in the treatment of rheumatoid arthritis is provided on pages 101-102.

(7) The presence or absence of working examples

The specification shows the activity of the instantly claimed compound in one very specific cell line. The in vitro data provided is very generic and does not show specific mechanisms of action of the instantly claimed compound. The data provided for rheumatoid arthritis on pages 101-102 provide some more detail, but specific IC50 data or population data or other data to support the use of the instantly claimed compound in the treatment of rheumatoid arthritis was not provided. It is well known that rheumatoid arthritis varies from patient to patient. The degree of the disease and treatment all differ.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role of the instantly claimed compounds in the treatment of rheumatoid arthritis and other related disorders, it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which patients with which diseases would benefit from which of the

many claimed compounds within the scope of the invention with a reasonable expectation of success.

The instant breadth of the claim(s) is broader than the disclosure, specifically, the instant claim is directed to the treatment of rheumatoid arthritis in general, but the specification, prior art or instant disclosure does not provide support for this or other related disorders.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 19-23 and 26-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification although enabling for a compound of formula (I), wherein the compound is a specific benzimidazole derivative, wherein a specific alkyl chain is present off the benzimidazole ring, it is not enabled for all definitions claimed without limitation, i.e. X, Z, Y, R1, R2, R3, R4, etc…

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Therefore, the claims are rejected because the compound and all the definitions are not enabled.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented (by the inventor);
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary (to make and/or use the invention).

The eight Wands factors are applied to the claims of the present invention below:

(1) The Nature of the Invention

The nature of the invention is a generic compound of formula (I), wherein there is no fixed core and the moieties are defined so broadly that it encompasses a vast number of compounds.

(2) The Breadth of the claims

The breadth of the claimed compounds are so broad that one of ordinary skill in the art could not ascertain all the possible combinations and subcombinations that could be made. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44

USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, the compounds of formula (I) yield an infinite number of combinations that when searched yielded hundreds of hits in STN.

(3) The state of the prior art

The state of the prior art is that benzimidazoles are well known in the art. They are commercially available. The patentability of the instantly claimed compounds is in the alkyl chain off the benzimidazole ring.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high. Only a target range of compounds would be synthesized and it is beyond the scope of one of ordinary skill in the art to have synthesized all of the potential number of compounds claimed.

(5) The predictability or unpredictability of the art

The compounds claimed in the instant application, wherein the moieties can be a number of different combinations include an extremely large scope of the potential compounds rendering the prior art unpredictable for making or using products as claimed on such a grand scale.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses chemical examples of the species of the compounds of formula (I), wherein the core is a benzimidazoel and there is an alkyl chain off the benzimidazole ring. The process of making the instantly claimed compounds of formula (I) produce benzimidazole compounds only.

(7) The presence or absence of working examples

The specification has no working examples of where the core compound is anything other than a benzimidazole.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for any of the extremely large number of compounds that would be encompassed by the claims, it would cause a skilled artisan an undue amount of experimentation to determine which product the claims were describing. A skilled artisan would not be able to predict if the instantly claimed products could be made or how they would be made because of the lack of guidance in the specification. In addition, a skilled artisan could not predict if the additional combinations would have the same utility as the instantly enabled compounds. Therefore, to overcome this rejection, the scope of the compound of formula (I) should be defined to those compounds with support in the specification.

Obviousness Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

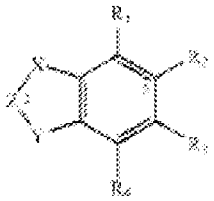
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-23 and 26-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-27 of US Pat App No 12/158,563 (no PGPUB number available).

Instant claim 1 claims

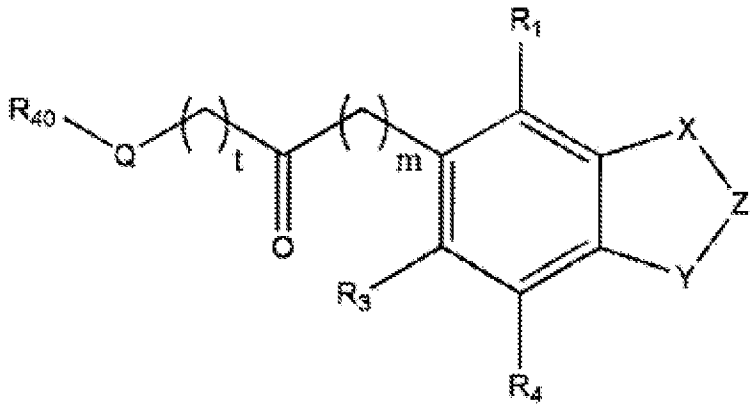
1. (original) A method of inhibiting cytokine or biological activity of MIF comprising contacting MIF with a cytokine or biological activity inhibiting effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof



(I)

The `563 App claims

(Currently amended) A method of treating, diagnosing or preventing autoimmune diseases, tumours, or chronic or acute inflammatory diseases comprising administering a treatment, prevention or diagnostic effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof to a subject in need thereof wherein:



The difference between the applications and the instant claims is that the instant claim is broader in scope than the copending application.

Although the conflicting claims are not identical, they are not patentably distinct from each other because one of ordinary skill in the art would recognize that the species claimed in the copending application can be made from the process disclosed in the instant application.

The motivation to optimize this class of compounds is the expectation that they will have similar pharmacological properties.

In the absence of showing unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention when faced with the prior filed applications that the instantly claimed compounds would be known.

The instant obviousness rejection is based on the close structural similarity of the instantly claimed compounds to the prior filed application compounds and the common utility shared among the compounds. There is an expectation among those of ordinary skill in the art that similar structural compounds will have similar properties and that modification of a known structure is mere experimentation within the means of a skilled artisan. See MPEP 2144.09(I). Therefore, claims 1-23 and 26-30 are rejected as obvious over the prior art.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susannah Chung, 11/18/08

/REI-TSANG SHIAO /
Primary Examiner, Art Unit 1626